REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 48-59 and 62-68 are in the case.

I. ELECTION/RESTRICTION

The election of Group I is affirmed. Claims 60, 61 and 69 have been canceled without prejudice.

II. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 54-59 stand provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 31, 32 and 38-41 of copending Application Serial No. 09/930,494. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

III. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 48-59 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons stated on page 7 of the Action dated October 22, 2003. The Examiner asserts that the phrase "a pyrimidine nucleotide precursor" renders all claims in which that language appears indefinite. The Examiner asserts that, in the absence of distinct chemical core, distinct language to describe the structural modifications, or the chemical names of precursor compounds of this invention, the identity of the precursors would be difficult to describe. The Examiner further asserts that the metes and bounds of the precursor compounds applicant regards as the

invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims. The rejection is respectfully traversed.

The phrase "a pyrimidine nucleotide precursor" is not indefinite to one of ordinary skill in this art. The term is defined at page 7 of the application as filed, and numerous examples are provided. Moreover, this terminology appears in the claims of commonly assigned issued U.S. patent 6,329,350.. Based on this, and the level of ordinary skill in this art, the reader would have no difficulty in understanding the phrase "a pyrimidine nucleotide precursor" as used in the present claims. Withdrawal of the 35 USC 112, second paragraph, rejection is accordingly respectfully requested.

IV. THE OBVIOUSNESS REJECTION

Claims 48-59 and 62-68 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al (1997) in combination with U.S. 6,316,426 to von Borstel et al. This rejection is respectfully traversed.

On page 6 of the Action, the Examiner asserts that Page discloses treatment of patients described with a syndrome including developmental delay and other conditions, and notes that Page differs from the presently claimed invention in that Page does not disclose the use of acyl derivatives of uridine, and does not explicitly disclose all the conditions within the scope of the presently claimed invention. The Examiner takes the position that these deficiencies in Page are rendered obvious by von Borstel because von Borstel describes a family of uridine and cytidine derivatives for the treatment of a variety of disorders including heart, muscle, plasma, liver, bone, diabetic, and neurological conditions (column 8, lines 20-24). Based on this, the Examiner concludes

that it would have been obvious to treat patients having a mitochondrial disease with an acylated derivative of uridine. The Examiner further states that "applicant has merely found a new property of the instant uridine compounds and such a discovery does not constitute a new use.", because, in the present case, the population to be treated is a subject having a mitochondrial disease and the prior art discloses the treatment of this population with an acylated derivative of uridine, rendering the instantly claimed method *prima facie* obvious.

At the outset, the Examiner's statement that "applicant has merely found a new property of the instant uridine compounds and such a discovery does not constitute a new use." is wrong. It is well established that patent protection may be secured in the United States for the discovery of a new or non-obvious property of a compound by way of method of treatment claims. Thus, the Examiner's characterization of the present invention as the "mere discovery of a new property" does not mean that patent protection cannot be secured. As will be clear from the arguments presented below, the present invention as claimed is not rendered obvious by the combined disclosures of Page and von Borstel.

The Examiner's position with respect to unpatentability appears to be based, in part, on the idea that overlap of conditions described by Page and von Borstel gives rise to a *prima facie* case of obviousness. However, overlapping symptoms are insufficient to establish a *prima facie* case of obviousness, because it is well recognized that unrelated diseases can have overlapping symptoms. It follows, therefore, that the effectiveness of a particular drug in treating a symptom in one disorder does not

necessarily, or even generally, imply that the drug will be useful in treating other diseases with similar symptoms.

For example, epilepsy or related seizure disorders may be caused by tumors, poisons, mitochondrial defects, or simply self-amplifying circuits of neural activity without other organic defects causing the seizures. Seizure episodes in a susceptible person can be triggered by progesterone deficits, e.g. associated with the menstrual cycle. Although the clinical symptoms – seizures – may look similar, the treatments will vary according to the underlying problem.

Valproate (Depakote) is a widely-used anti-seizure medication, but it can actually exacerbate seizures (and other manifestations of mitochondrial disease) caused by mitochondrial deficits, due to its inhibitory effect on mitochondrial respiration. For someone with seizures triggered by a progesterone deficit, progesterone or an analog thereof is more appropriate than increased doses of other anti-seizure medications, which have debilitating side effects at higher doses. Some seizure disorders associated with foci of hyperexcitable neurons are best treated with electrodes inserted into the brain, which would be inappropriate for seizures caused by metabolic deficits. As further evidence of this, attached are copies of the following papers which are briefly discussed below.

Lam et al (Eur J Pediatr. 1997 Jul;156(7):562-4. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Lam CW, Lau CH, Williams JC, Chan YW, Wong LJ. Department of Pathology, Princess Margaret Hospital, Lai Chi Kok, Hong Kong) have reported that:

"...valproate should not be given to patients suspected of having mitochondrial diseases. In addition, for patients whose seizures worsen with valproate therapy, an inborn error of mitochondrial metabolism should be suspected. The underlying mitochondrial DNA defects should be sought for family screening and genetic counselling."

Likewise, Krahenbuhl et al (Liver. 2000 Jul;20(4):346-8; Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. Krahenbuhl S, Brandner S, Kleinle S, Liechti S, Straumann D. Department of Clinical Pharmacology, University of Berne, Switzerland) have reported that "Mitochondrial diseases should therefore be considered as a risk factor for valproate-induced liver failure and be excluded before treatment with valproate."

Another example of a condition which can arise from different causes is arthritis. Pain in the joints can be caused by autoimmune attack (rheumatoid arthritis, psoriatic arthritis, or lupus-associated), osteoarthritis, infections, e.g. lime disease, gout, deposition of antibody complexes, etc. All of these disorders may present with joint pain as a predominant symptom, but the appropriate treatments are very different for each of these different diseases that underlie similar symptoms, e.g. anti-TNF therapies for rheumatoid arthritis, B-Cell suppressors for Lupus, nonsteroidal anti-inflammatory drugs for osteoarthritis, antibiotics for Lyme disease, allopurinol for gout. Attention in this regard is directed to Ritchie et al., "Diagnostic Approach to Polyarticular Joint Pain", *American Family Physician*, 68, 6, 1151-1160 (2003) (copy attached), which states (in the Abstract) that "Identifying the cause of polyarticular joint pain can be difficult because of the extensive differential diagnosis." As a consequence, "...family physicians need to keep the diagnosis open in evaluating patients who present with pain in multiple joints." (page 1151, left hand column).

Many other examples are possible in which symptoms themselves provide inadequate information for determining their cause and appropriate treatment. Developmental delays may arise from a variety of underlying causes, including metabolic defects such as phenylketonuria, lead or mercury poisoning, epilepsy, or a variety of genetic defects. A diet low in phenylalanine helps patients with phenylketonuria (in which an enzyme deficiency prevents phenylalanine metabolism), but is useless in other conditions involving developmental delay or seizures. Lead and mercury poisoning can perhaps helped by administration of chelating agents which are useless in diseases not caused by heavy metals. Antiepileptic drugs like valproate or lamictal can help developmental delays secondary to disruptions in brain function caused by seizures, but may be detrimental in disorders not caused by seizures.

The relationship between the molecular anomaly, 5'-nucleotidase excess, and symptoms in the children described by Page et al. is not clear. As the authors point out, the disorder is not associated with actual uridine nucleotide deficits (and the symptoms do not match those of the only known pyrimidine deficit disorder, Orotic Aciduria). Uridine and related pyrimidine compounds were initially tested in these patients because the first one identified presented with megaloblastic anemia (a primary symptom of orotic aciduria), which was later attributed to her anti-seizure medication. The finding that uridine was helpful was actually fortuitous and does provide a basis for asserting that uridine would be helpful in similar symptoms or symptom complexes associated with other diseases.

In addition, the cited Page et al paper is not the first publication of the use of uridine to treat 5'-nucleotidase excess. This was published earlier in Page, et al., "A

Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348. (of record). The fact that between 1991 and the subject invention no one used uridine compounds to treat pathophysiological consequences of mitochondrial respiratory chain dysfunction is further evidence of its nonobviousness.

Prior to the effective filing date of the subject application, a number of diseases were known to be mitochondrial in origin. Yet they were not treated with pyrimidine nucleotide precursors. This observation refutes the Office's position that it would have been obvious to treat any and all mitochondrial diseases using pyrimidine nucleotide precursors. As evidence, applicants submit the following journal articles:

DiMauro, et al, "Mitochondrial encephalomyopathies: where next?", Revista de Neurologia (1999) 28(2):164-168.

Luft, "Review: The development of mitochondrial medicine", Proc. Natl. Acad. Sci. USA (September 1994) 91: 8731-8738.

Beal, "Mitochondrial dysfunction in neurodegenerative diseases", Biochimica et Biophysica Acta (1998) 1366: 211-223.

Blass, "Brain metabolism and brain disease: is metabolic deficiency the proximate cause of Alzheimer dementia", J. Neurosc. Res. (2001) 66: 851-856.

Bowling, et al., "Minireview: Bioenergetic and Oxidative stress in neurodegenerative diseases", Life Sciences (1995) 56(14): 1151-1171.

Beal, "Mitochondria, free radicals, and neurodegeneration", Current Opinion Neurobiol. (1996) 6: 661-666.

Browne, et al, "Oxidative damage and mitochondrial dysfunction in neurodegenerative diseases", Biochem. Soc. Trans. (1994) 22: 1002-1006.

Schulz, et al., "Mitochondrial dysfunction in movement disorders", Current Opinion in Neurology (1994) 7:333-339.

In view of the above, it is clear that a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the obviousness rejection is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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